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(54) Title: TREATMENT OF GASTRIC ASTHMA

(57) Abstract

Use of neurokinin 2 (NK2) receptor antagonists in the treatment or prevention of gastric asthma or adverse respiratory events associated with gastroesophageal reflux, including pharmaceutical compositions containing the NK2 receptor antagonist and methods for making such compositions.

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TREATMENT OF GASTRIC ASTHMA

Background

Gastric asthma, described by Bruno et al. (Int. J. IMPH. 10/3: 195-204, 1997; Mays, E.E. JAMA 236: 2626, 1976), is a syndrome arising from the gastroesophageal acid induced changes in respiratory function. There is a progressive body of evidence supporting the role of gastroesophageal reflux as a triggering factor of bronchial hyperreactivity leading to this syndrome.

The mammalian neurokinins comprise a class of peptide neurotransmitters which are found in the peripheral and central nervous systems. The three principal neurokinins are Substance P (SP), Neurokinin A (NKA) and Neurokinin B (NKB). There are also N-terminally extended forms of at least NKA. At least three receptor types are known for the three principal neurokinins. Based upon their relative selectivities favoring the neurokinin agonists SP, NKA and NKB, the receptors are classifed as neurokinin 1 (NK1), neurokinin 2 (NK2) and neurokinin 3 (NK3) receptors, respectively. In the periphery, SP and NKA are localized in C-afferent sensory neurons, which neurons are characterized by non-myelinated nerve endings known as C-fibers, and are released by selective depolarization of these neurons, or selective stimulation of the C-fibers. C-Fibers are located in the airway epithelium, and the tachykinins are known to cause profound effects which clearly parallel many of the symptoms observed in asthmatics. The effects of release or introduction of tachykinins in mammalian airways include bronchoconstriction, increased microvascular permeability, vasodilation, increased mucus secretion and activation of mast cells. Thus, the tachykinins are implicated in the pathophysiology and airway hyperresponsiveness observed in asthmatics; and blockade of the action of released tachykinins may be useful in the treatment of asthma and related conditions.

Accordingly, NK2 antagonists have been implicated in the pathology of numerous diseases including asthma, airway oedema, bladder hypermotility, hypertension, pain, gastrointestinal-hypermotility, psychoses including schizophrenia and other psychatric indications, such as depression and anxiety.

The development of antagonists for the NK2 receptor has been purported to be useful for treatment of bronchial reactivity (Barnes, P.J. Lancet, i: 242-245, 1986). Although the etiological relationship between gastroesophageal reflux and asthma is not clear, the number

of reflux episodes can be correlated to those of bronchial hyperreactivity (Vincent et al.,Eur. Respir. J. 10/10: 2255-2259, 1997). Current asthma therapies have not been shown to reverse bronchial hyperreactivity and in some cases are associated with adverse side effects (steroids), the progressive diminution of the therapeutic benefits (beta agonists) and they have not been shown to have any beneficial effects for gastroesophageal reflux induced respiratory changes. Moreover, chronic asthma treatments such as theophylline and beta agonists may promote or worsen gastroesophageal reflux (Bruno et al., Int. J. IMPH. 10/3: 195-204, 1997). Therefore, there is an unmet medical need for a treatment that interrupts the cyclic nature of gastroesophageal reflux and asthma.

There are no suggestions that NK2 antagonists could be beneficial in treating gastric asthma and in particular in treating gastric asthma associated with gastroesophageal reflux, which is manifested in adverse respiratory events such as chronic cough and asthma. The use of NK2 antagonists minimises the possibility of side-effects associated with alternative methods of treating such disease conditions and offers the physician a valuable alternative treatment regime.

Summary of the Invention

The present invention relates to use of compounds that antagonise the pharmacological actions of the endogenous neurokinins, particularly at the NK2 receptor, and compositions containing them, in treating the aforementioned disease conditions and, in particular, gastric asthma.

Brief Description of the Drawings

The accompanying drawings incorporated in and forming part of the specification illustrates principles of the invention. In the drawings:

Figure 1 is a graph representing the effect of tachykinin antagonism on esophageal-acid-induced bronchoconstriction; and

Figure 2 is a graph representing the effect of Example 1 on HCl infusion into allergic Guinea pigs.

Description

The present invention provides a method of treating gastric asthma in a patient in need thereof with an effective amount of an NK2 receptor antagonist.

In another aspect the present invention provides a method of treating adverse respiratory events associated with gastroesophageal reflux in a patient in need thereof with an effective amount of an NK2 receptor antagonist.

In yet another aspect the present invention provides the use of an NK2 receptor antagonist in a method of manufacture of a medicament for the treatment of gastric asthma.

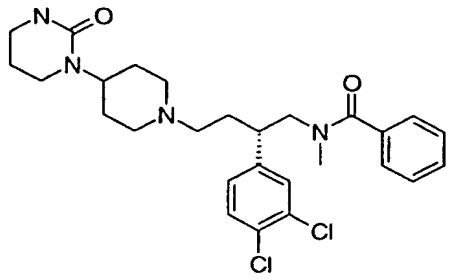
In yet another aspect the present invention provides the use of an NK2 receptor antagonist in a method of manufacture of a medicament for the treatment of treating adverse respiratory events associated with gastroesophageal reflux.

In yet a further aspect the present invention provides an NK2 receptor antagonist for use in the treatment of gastric asthma or for the treatment of treating adverse respiratory events associated with gastroesophageal reflux.

Compounds with NK2 receptor antagonist properties are known in the scientific and patent literature, for example in WO9719060, EPA739891, WO9624582, EPA709376, EPA709375, EPA680962, WO9516682, WO9515961, WO9512577, WO9505377, EPA630887, EPA625509, WO9314084, WO9605193, WO9422822 and many other patent applications.

Preferred NK2 receptor antagonists are SR-48968, SR-144190, YM-38336, MEN-10627, MEN-11420, GR-159897, RPR-106145, PD-147714, FK-224, MDL-105212A, MDL-105172A, L-743986, S-16474 (all reviewed by von Sprecher et al (IDrugs, 73 (1998)) and the compounds of WO9512577.

A particularly preferred compound is (S)-N-[2-(3,4-dichlorophenyl)-4-[4-(2-oxoperhydropyrimidin-1-yl)piperidino]butyl]-N-methyl-benzamide of the formula (I) or a pharmaceutically acceptable salt thereof, such as the dihydrochloride.



(I)

which is disclosed in WO9512577.

NK2 receptor antagonists may be prepared according to the references or by standard literature methods. It is well known in the art how to test a compound to assess whether it is an NK2 receptor antagonist, for example see assays in the aforementioned patent applications such as in WO9512577.

In order to use an NK2 antagonist for the therapeutic treatment of gastric asthma (including prophylactic treatment) of mammals including humans, it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

Therefore, in another aspect, the present invention provides a method of treating gastric asthma in a patient in need thereof with a pharmaceutical composition comprising an effective amount of an NK2 receptor antagonist.

In a further aspect the present invention provides a pharmaceutical composition comprising an NK2 receptor antagonist for use in the treatment of gastric asthma.

Pharmaceutical compositions comprising an NK2 antagonist may be administered in standard manner, for example by oral, parenteral, buccal, nasal adminstration or by inhalation or insufflation. For these purposes the compounds of this invention may be formulated by means known in the art into the form of, for example, tablets, capsules, aqueous or oily solutions, suspensions, emulsions, gels, nasal sprays, finely divided powders or aerosols or nebulisers for inhalation, and for parenteral use (including intravenous, intramuscular or infusion) sterile aqueous or oily solutions or suspensions or sterile emulsions.

The pharmaceutical composition comprising an NK2 antagonist may also contain, or be co-administered (simultaneously or sequentially) with, one or more pharmacological agents of value in treating gastric asthma or a related or associated disease.

The pharmaceutical composition will normally be administered to humans so that, for example, a daily dose of 0.01 to 25 mg/kg body weight (and preferably of 0.1 to 5 mg/kg body weight) of compound is received. This daily dose may be given in divided doses as necessary, the precise amount of the compound received and the route of administration depending on the weight, age and sex of the patient being treated and on the particular disease condition being treated according to principles known in the art.

Typically, unit dosage forms will contain about 1 mg to 500 mg of a compound. For example a tablet or capsule for oral administration may conveniently contain up to 250 mg (and typically 5 to 100 mg) of a compound. In another example, for administration by inhalation, a compound may be administered in a daily dosage range of 5 to 100 mg, in a

single dose or divided into two to four daily doses. In a further example, for administration by intravenous or intramuscular injection or infusion, a sterile solution or suspension containing up to 10% w/w (and typically 5% w/w) of a compound.

It has been demonstrated that tracheal plasma extravasation, a feature of asthma, induced by esophageal acid can be prevented by blockade of NK1 receptors (Hamamoto et al., J. Appl. Physiol. 82/3: 738-745, 1997). In a particular aspect therefore, treatment of gastric asthma with an NK2 receptor antagonist may be augmented with an NK1 receptor antagonist; alternatively, gastric asthma may be treated with a single compound containing dual antagonist activity against both receptors. Therefore, in one aspect an NK2 antagonist may be co-administered with an NK1 antagonist with the advantage of blocking both neurogenic inflammation (plasma extravasation, edema, and mucous secretion) and bronchial hyperreactivity In another aspect the NK2 antagonist for use in this invention is also capable of antagonism at the NK1 receptors. That is, the compound for use in this invention is capable of antagonising the actions of both NK1 and NK2 receptors. Such compounds are known from the literature and may include compounds within the patent applications mentioned above as well as for example compounds within WO9610568, EPA733632, WO9637489, EPA699674, WO9722597, WO9628441, WO9827085, WO9834949, EPA776893, FRA2729952, FRA2729953, FRA2729954, WO9719926, WO9721680, WO9818761, WO9820010, WO28297, WO9634857, WO9634864, WO9639386, WO9827086, WO9714671, WO9898076694, WO9719942, WO9807722, WO9605193, WO9727188, WO9705110, EPA790248, EPA791592 and USP 5688960, 5696267, 5789422, 5691362, 5719147 and 5807865.

Therefore, in a further aspect, the present invention provides a method of treating gastric asthma in a patient in need thereof with an effective amount of an NK1/NK2 receptor antagonist.

In another aspect the present invention provides the use of an NK1/NK2 receptor antagonist in a method of manufacture of a medicament for the treatment of gastric asthma.

In yet a further aspect the present invention provides an NK1/NK2 receptor antagonist for use in the treatment of gastric asthma.

Gastroesophageal reflux, also known as heartburn, is a widespread disorder which affects millions of adults and children. Gastroesophageal reflux has been described as the retrograde movement of stomach contents into the esophagus. This is clearly discomforting.

If gastroesophageal reflux is not treated more severe disease conditions may occur such as esophagitis, ulceration, hemorrhage and related conditions. It has been estimated that approximately 40% of asthmatics suffer from gastroesophageal reflux. The aspiration of gastric contents into the airway or a vagal reflex arising from the esophagus may result in bronchoconstriction, as described by Harding and Richter, Chest. 111, 1359 (1997).

Gastroesophageal reflux is presently treated by antacids, histamine H_2-antagonists or proton pump inhibitors such as omeprazole. Relapse is common, regardless of therapy.

In another aspect the present invention provides an NK2 receptor antagonist for treating gastroesophageal reflux and in particular for the treatment of the adverse respiratory events such as chronic cough and asthma associated with gastroesophageal reflux.

The present invention is illustrated by the tests and results hereinbelow.

NK_1 and NK_2 In Vivo Functional Assay

The activity of a compound as an antagonist of NK1 and/or NK2 receptors may be demonstrated in vivo in laboratory animals as described in: Buckner et al. "Differential Blockade by Tachykinin NK1 and NK2 Receptor Antagonists of Bronchoconstriction Induced by Direct-Acting Agonists and the Indirect-Acting Mimetics Capsaicin, Serotonin and 2-Methyl-Serotonin in the Anesthetized Guinea Pig." J. Pharm. Exp. Ther.,1993, Vol 267(3), pp. 1168-1175. For experiments measuring the effects of infused acid into the esophagus on bronchoconstriction :

Compounds are tested in anesthetized guinea pigs pretreated with i.v. indomethacin (10 mg/kg, 20 min) and propranolol (0.5 mg/kg, 15 min). In some experiments thiorphan (10 mg/kg ,10 min), atropine (1 mg/kg, 25 min), 1-(α-(2-isopropoxyphenyl)aceto)-3-(4-phenylquinuclidin-1-yl)-3*R*-(3,4-dichlorophenyl)piperidine (1 μmol/kg, 25 min), Example I (various doses, 30 min) or their combination are also administered i.v. Saline (pH 5.5) or HCl (pH 0-1) is infused (0.5 ml over 1 min) into the esophagus. The infusate is confined to the esophagus due to ligations at the proximal and distal ends. Pulmonary resistance (a measure of bronchoconstriction) is monitored for at least thirty minutes after cessation of the infusion. Peak resistance values during the monitored period are then determined and expressed as a percentage of the baseline pulmonary resistance before the esophageal infusion.

For experiments measuring the effects of infused acid into the esophagus on tracheal plasma extravasation (edema) :

Compounds are tested in anesthetized guinea pigs pretreated with i.v. 1-(α-(2-isopropoxyphenyl)aceto)-3-(4-phenylquinuclidin-1-yl)-3*R*-(3,4-dichlorophenyl)piperidine (3 μmol/kg, 25 min) or its vehicle, atropine (1 mg/kg, 25 min) indomethacin (10 mg/kg, 20 min), propranolol (0.5 mg/kg, 15 min), HOE-140 (0.1 μmol /kg, 12 min), thiorphan (10 mg/kg, 10 min) and Evans blue dye (30 mg/kg, 0 min). Saline (pH 5.5) or HCl (pH 0-1) is infused (0.5 ml over 1 min) into the esophagus. The infusate is confined to the esophagus due to ligations at the proximal and distal ends. Ten minutes following the esophageal infusion guinea pigs are perfused via the aorta (120 ml saline over 2 min) to remove intravascular dye. A section of trachea (1 cm) immediately caudal to the carina is removed, trimmed, weighed, and incubated in formamide for 18 hr at 60 ° C. The dye content of the tissue is then determined by measuring Absorbance, at 620 nm, of the resulting formamide/Evans blue solution and converting this value into ng Evans blue/mg trachea via a standard curve.

Results of testing of (S)-N-[2-(3,4-dichlorophenyl)-4-[4-(2-oxoperhydropyrimidin-1-yl)piperidino]butyl]-N-methyl-benzamide (formula (I)) are as follows. 1-(α-(2-Isopropoxyphenyl)aceto)-3-(4-phenylquinuclidin-1-yl)-3*R*-(3,4-dichlorophenyl)piperidine is a known selective NK1 antagonist.

The graphs in Figures 1 and 2 clearly demonstrate that the NK2 receptor antagonist (Example I), either alone or in combination with the other treatments, is capable of completely inhibiting the increase in pulmonary resistance (i.e. bronchoconstriction) resulting from the infusion of 1 N HCl into the esophagus of guinea pigs (top graph). The muscarinic antagonist, atropine, or the NK1RA, 1-(α-(2-Isopropoxyphenyl)aceto)-3-(4-phenylquinuclidin-1-yl)-3*R*-(3,4-dichlorophenyl)piperidine, either alone or concomitantly have no effect on this increase in resistance (top graph). Even in an allergic, hyperreactive state (OA sensitized), as is often the case in asthma, NK2 receptor antagonism is able to anatagonize the adverse pulmonary effects of infused acid (bottom graph). This experimental data is representative of the effects of acid reflux in the esophagus of human asthmatics suffering from "gastric asthma" and illustrates the anticipated benefit of NK2 receptor antagonists in treating this syndrome.

Examples

The following illustrates representative pharmaceutical dosage forms which may be used for the therapeutic or prophylactic administration of NK1 antagonists or pharmaceutically-acceptable salt or in vivo hydrolysable ester thereof hereinafter referred to as 'Compound X'):

(i)	Tablet 1	mg/tablet
	'Compound X'	100.0
	Lactose	77.5
	Providone	15.0
	Croscarmellose sodium	12.0
	Microcrystalline cellulose	92.5
	Magnesium stearate	3.0
		300.0

(ii)	Tablet 2	mg/tablet
	'Compound X'	20.0
	Microcrystalline cellulose	410.0
	Starch	50.0
	Sodium starch glycolate	15.0
	Magnesium stearate	5.0
		500.0

(iii)	Capsule	mg/capsule
	'Compound X'	5.9
	Lactose	392.9
	Sodium lauryl sulphate	1.2
		400.0

(iv)	Capsule 2	mg/capsule
	'Compound X'	29.6
	Lactose	331.4
	Sodium Lauryl Sulphate	1.0
		362.0

(v)	Injection 1 (1mg/mL)	mg/mL
	'Compound X' (free acid form)	1.0

Dibasic sodium phosphate	12.0
Monobasic sodium phosphate	0.7
Sodium chloride	4.5
1.0 N Sodium hydroxide solution	q.s
(pH adjustment to 7.0-7.5)	
Water for injection	q.s. ad 1 mL

(vi) Injection 2 (10 mg/mL)

	mg/mL
'Compound X' (free acid form)	10.0
Monobasic sodium phosphate	0.3
Dibasic sodium phosphate	1.1
Polyethylene glycol 400	200.0
0.1 N Sodium hydroxide solution	q.s.
(pH adjustment to 7.0-7.5)	
Water for injection	q.s. ad 1 mL

(vii) Aerosol

'Compound X'	1g
HFA 227 or HFA 134A with 5% ethanol	

It will be appreciated that the above pharmaceutical compositions may be varied according to well-known pharmaceutical techniques to accommodate differing amounts and types of active ingredient 'Compound X'. The aerosol (vii) may be used in conjunction with a standard, metered dose aerosol dispenser.

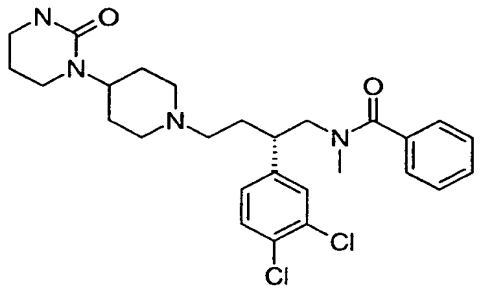
CLAIMS

1. The use of an NK2 antagonist for treating or prevention of a condition in a patient in need thereof, comprising the step of administering a therapeutically-effective amount of the NK2 receptor antagonist, wherein the condition is gastric asthma or adverse respiratory events associated with gastroesophageal reflux.

2. A use according to Claim 1 additionally comprising the step of administering a NK1 antagonist.

3. A use according to Claim 1 wherein the NK2 antagonist is also an NK1 antagonist.

4. A method according to any of Claim 1 or 2 wherein the NK2 antagonist has the structure



5. Use of an NK2 receptor antagonist for the manufacture of a medicament for the treatment or prevention of a condition, wherein the condition is gastric asthma or adverse respiratory events associated with gastroesophageal reflux.

6. A use according to any one of Claims 1, 2, 3 or 5 wherein the condition is gastric asthma.

7. A use according to any one of Claims 1, 2, 3 or 5 wherein the condition is adverse respiratory events associated with gastroesophageal reflux.

8. An oral pharmaceutical composition for the treatment of a condition, the composition comprising:

a therapeutically-effective amount of an NK2 antagonist; and

a diluent or carrier;

wherein the condition is gastric asthma or adverse respiratory events associated with gastroesophageal reflux.

9. A composition according to Claim 8 wherein the condition is gastric asthma.

10. A composition according to Claim 8 wherein the condition is adverse respiratory events associated with gastroesophageal reflux.

Fig.1.

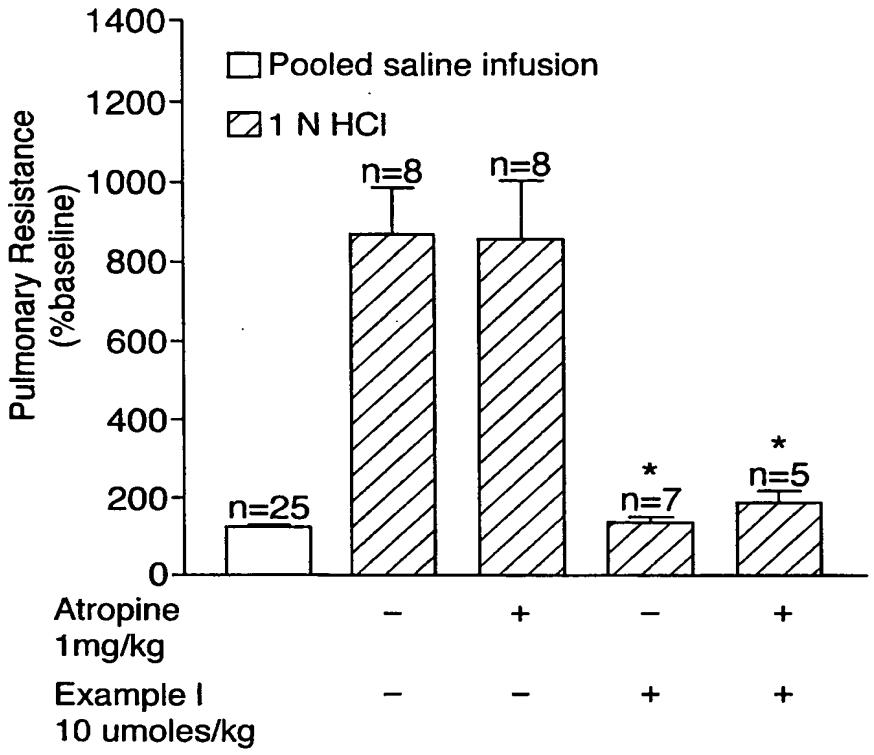
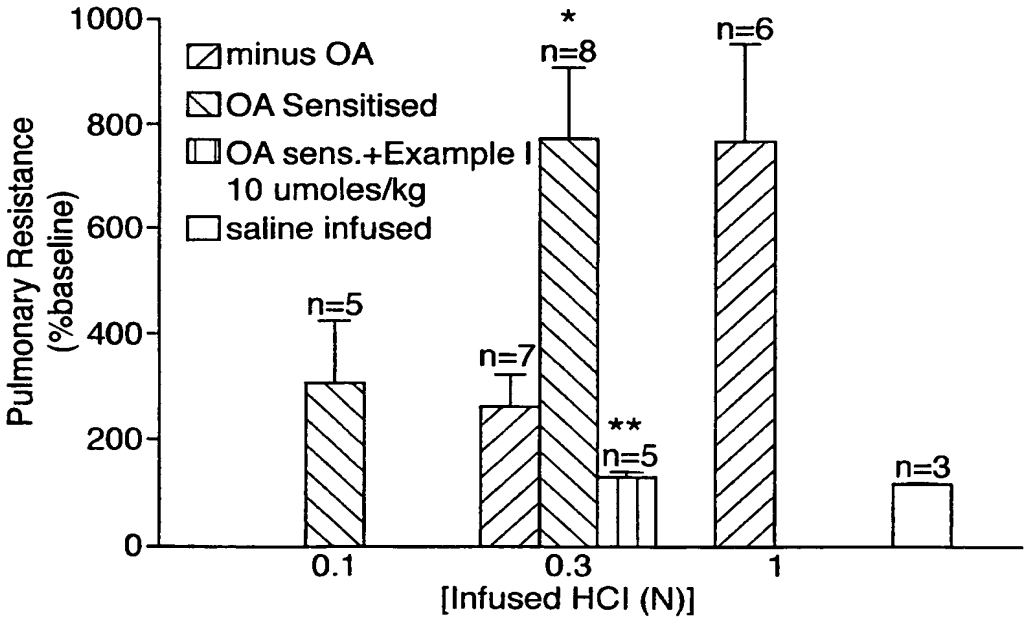

1400
1200
1000
800
600
400
200
0
Pulmonary Resistance (%baseline)
Pooled saline infusion
1 N HCl
n=8
n=8
n=25
*
n=7
*
n=5
Atropine 1mg/kg
– + – +
Example I 10 umoles/kg
– – + +

Fig.2.


1000
800
600
400
200
0
Pulmonary Resistance (%baseline)
minus OA
OA Sensitised
OA sens.+Example I 10 umoles/kg
saline infused
n=5
n=7
*
n=8
**
n=5
n=6
n=3
0.1
0.3
1
[Infused HCl (N)]

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(54) Title: USE OF NK ANTAGONIST FOR TREATING GASTRIC ASTHMA

(57) Abstract

Use of neurokinin 2 (NK2) receptor antagonists in the treatment or prevention of gastric asthma or adverse respiratory events associated with gastroesophageal reflux, including pharmaceutical compositions containing the NK2 receptor antagonist and methods for making such compositions.

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BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 99/03536

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/505 A61K31/00 A61K31/513 A61P11/06 A61P11/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data, BIOSIS, EMBASE, MEDLINE, SCISEARCH

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	WO 95 05377 A (ZENECA LTD) 23 February 1995 (1995-02-23) example 18 claim 7 claims 1-9 page 1, line 26 - line 32	7-10 1-6
X Y	EP 0 791 592 A (PFIZER LTD ;PFIZER RES & DEV (IE)) 27 August 1997 (1997-08-27) cited in the application page 2, line 8 - line 34 examples 1-9	7-10 1-3,5,6

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 June 2000	07/07/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Bonzano, C

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inter. ..ional Application No
PCT/GB 99/03536

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 12577 A (ZENECA LTD) 11 May 1995 (1995-05-11) cited in the application	7-10
Y	page 1, paragraph 1 - paragraph 3 page 42; figures 1,1C claim 1	1-3,5,6
X	EP 0 625 509 A (ZENECA LTD) 23 November 1994 (1994-11-23)	7-10
Y	page 2, line 1 - line 30	1-3,5,6
X	EP 0 630 887 A (ZENECA LTD) 28 December 1994 (1994-12-28)	7-10
Y	claims 1,9,11	1-3,5,6
X	WO 97 27185 A (MARCHINGTON ALLAN PATRICK ;MEADOWS SANDRA DORA (GB); MIDDLETON DON) 31 July 1997 (1997-07-31)	7-10
Y	claim 1	1-3,5,6
Y	US 5 697 112 A (COLAVITO BARBARA J ET AL) 16 December 1997 (1997-12-16) column 1, line 12	1-6
Y	MAYS: "Intrinsic asthma in adults" E.E.JAMA, vol. 236, no. 23, 1976, page 2626 XP000914287 page 2826, column 1 table 2	1-6
Y	KAVURU: "medical treatment..." GASTROESOPHAGEAL REFLUX DISEASE AND AIRWAY DISEASE, - 1999 pages 179-203, XP000920806 page 181, paragraph 2	1-6

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-3,5-10 relate to compounds defined by reference to a desirable pharmacological property, namely the activity as antagonist of NK1 or NK2 receptors.

The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is not fully possible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compounds by reference to their pharmacological profiles. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds structurally identified in claim 4, to those specifically disclosed in the description at page 3, lines 17-19, and to those described in the patents cited at page 3, lines 12-15 (as far as indexed by chemical abstracts), with due regard to the general idea underlying the present invention.
Claims searched completely: 4.
Claims searched incompletely: 1-3,5-10.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

information on patent family members

Inter onal Application No
PCT/GB 99/03536

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Inter ional Application No
PCT/GB 99/03536

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